

Appl. No. 10/016,850

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Appl. No. : 10/016,850 Confirmation No. 7435  
Applicant : HUGHES et al.  
Filed : December 14, 2001  
Title : PHARMACEUTICAL CONJUGATES WITH ENHANCED  
PHARMACOKINETIC CHARACTERISTICS  
  
TC/A.U. : 1600/1618  
Examiner : FAY, Z.  
  
Docket No. : D-3004  
Customer No. : 33197

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**APPEAL BRIEF**

Applicants hereby appeal from the Office Action of July 13, 2006, and argue as follows.

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**CERTIFICATE OF EXPRESS MAILING**

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office fax number 571-273-8300, or mailed by Express MailPost Office to Address bearing label no. EVS1744401545 to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Date: October 13, 2006  
Name: Walter M. Thoe

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**REAL PARTY IN INTEREST**

The inventors, Patrick M. Hughes and Orest Olejnik, each assigned their entire interest in this patent application to Allergan Sales, Inc. via an assignment document executed on December 10, 2001 and recorded with the United States Patent and Trademark Office at reel 023899, frame 0630. Allergan Sales, Inc. was subsequently merged with Allergan Sales, L.L.C. Allergan Sales, L.L.C. then assigned its entire interest in this application to Allergan, Inc.

Allergan, Inc. is therefore the owner of this patent application and the real party in interest in this appeal.

**RELATED APPEALS AND INTERFERENCES**

There are no related appeals or interferences.

**STATUS OF CLAIMS**

Claims 7, 10, 13, and 17-23 have been cancelled without prejudice to their possible later presentation in a continuation or divisional application.

Claims 1-6, 8, 9, 11, 12, 14-16 and 24-26 are currently pending and have been rejected and are under appeal.

**STATUS OF AMENDMENTS**

No amendments have been made since the mailing date of the Office Action of July 13, 2006.

**SUMMARY OF CLAIMED SUBJECT MATTER**

Claim 1 is drawn to a topical ophthalmic composition comprising a carrier and a pharmaceutical conjugate, wherein the carrier comprises an ophthalmically useful therapeutic component (TC) covalently coupled to an efficacy enhancing component (EEC) effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye. The efficacy-enhancing component comprises a specifically recited generic chemical structure. This claim is supported by the specification at, e.g., pages 2-3.

Claim 2 is drawn to the composition of claim 1 in which the TC and EEC are joined directly by a covalent bond and the carrier comprises a liquid. Support for this claim is as indicated for claim 1; in addition, support can be found at page 3, lines 21 and 22 and page 17, lines 9-11.

Claim 3 is drawn to the composition of claim 1 in which the TC and EEC are joined by a linker. Support for this claim is as indicated for claim 1; in addition, support can be found at page 3, lines 22-24.

Claim 4 is drawn to the composition of claim 1 wherein R1 and R2 are H and R3 is a linker. Support for this claim is as indicated for claim 1; in addition, support can be found at page 12, lines 22 and 23.

Claim 5 is drawn to the composition of claim 1 wherein the efficacy enhancing component is a memantine. Support for this claim is as indicated for claim 1; in addition, support can be found at page 12, lines 23 and 24.

Claim 6 is drawn to the composition of claim 1 wherein the linker is selected from a Markush group of linkers. Support for this claim is as indicated for claim 1; in addition, support can be found at page 4.

Claim 8 is drawn to the composition of claim 1 wherein the therapeutic component is selected from the group consisting of quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and mixtures thereof. Support for this claim is as indicated for claim 1; in addition, support can be found at page 9, line 31 to page 10, line 3.

Claim 9 is drawn to the composition of claim 1 wherein the efficacy-enhancing component comprises a memantine, and the conjugate further comprises a linker joining the therapeutic component and the memantine. Support for this claim is as indicated for claim 1; in addition, support can be found at page 12, lines 23 and 24 and page 3, lines 22-24.

Claim 11 is drawn to the composition of claim 8 wherein the efficacy-enhancing component comprises a memantine, and the conjugate further comprises a linker joining the therapeutic component and the memantine. Support for this claim is as indicated for claim 8; in addition, support can be found at page 12, lines 23 and 24 and page 3, lines 22-24 and page 14, lines 32-34.



Claim 12 is drawn to the composition of claim 1 wherein the therapeutic component and the efficacy enhancing component disassociate under physiological conditions. Support for this claim is as indicated for claim 1; in addition, support can be found at page 14, lines 4-6.

Claim 14 is drawn to the composition of claim 1 wherein the conjugate has an aqueous solubility, a partition coefficient and/or an affinity for melanin that is greater relative to a compound comprising the same therapeutic component which is not joined to an efficacy enhancing component. Support for this claim is as indicated for claim 1; in addition, support can be found at page 11, lines 3-7 and Example 6.

Claim 15 is drawn to the composition of claim 1 wherein the conjugate is a salt. Support for this claim is as indicated for claim 1; in addition, support can be found at page 11, line 15-28.

Claim 16 is drawn to a topical ophthalmic composition comprising a carrier and a pharmaceutical conjugate, wherein the carrier comprises an ophthalmically useful therapeutic component (TC) covalently coupled via a linker to an efficacy enhancing component (EEC) effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye. The efficacy-enhancing component comprises a specifically recited generic chemical structure, as is the linker. This claim is supported by the specification at, e.g., pages 2-4.

Claim 24 is drawn to a topical ophthalmic composition comprising a carrier and a pharmaceutical conjugate, wherein the carrier comprises an ophthalmically useful therapeutic component (TC), comprising a ophthalmically useful quinoxoline component, covalently coupled via a linker to an efficacy enhancing component (EEC) effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye. The efficacy-enhancing component and linker each comprise specifically recited generic chemical structures. This claim is supported by the specification at, e.g., pages 2-4 and page 9, line 31 to page 10, line 3.

Claim 25 is drawn to the composition of claim 24 wherein the therapeutic component is selected from the group consisting of quinoxaline, (2-imidazolyl-2-ylamino) quinoxaline, 5-bromo-6-(2-imidazolyl-2-ylamino) quinoxaline, and mixtures thereof. This claim is supported by the specification at, e.g., pages 2-4 and page 9, line 31 to page 10, line 3.

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Claim 26 is drawn to the composition of claim 25 wherein the therapeutic component comprises brimonidine tartrate. Support for this claim is as indicated for claim 25 and at page 17, line 32.

**GROUND OF REJECTION TO BE REVIEWED ON APPEAL**

Pending claims 1-6, 8, 9, 11, 12, 14-16 and 24-26 have been rejected as allegedly unpatentable under 35 U.S.C. § 103(a) over the combination of DeSantis (U.S. Patent Publication 2001/0047012) and Collins et al., (WO 01/92288).

ARGUMENT

I. Rejections Pursuant to 35 U.S.C. §103(a)

A) Did the Examiner err by finding that claims 1-6, 8, 9, 11, 12, 14-16 and 24-26 are obvious over Desantis (U.S. Patent Publication 2001/0047012) and Collins et al., (WO 01/92288)?

i) Claims 1-6, 8, 9, 11, 12, and 14-16.

*a) Did the examiner err by finding that the presently claimed topical ophthalmic compositions targeted to the posterior segment of the eye are obvious over DeSantis, which describes treating glaucoma and elevated IOP with a combination of an anterior segment-acting IOP-lowering agent and a glutamate antagonist, and Collins, which discloses conjugates comprising antibiotic agents targeted to infectious tissue.*

1) The combination of DeSantis and Collins teach away from a conjugate comprising a therapeutic agent and an admantidine moiety targeting the posterior segment of the eye.

A patent claim is in violation of 35 U.S.C. §103(a) if the difference between the teachings of the prior art and of the claimed invention when taken as a whole are such that a person of ordinary skill in the art would find the claimed invention obvious in light of the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (S.Ct. 1966).

The present invention is directed to a topical ophthalmic composition comprising a conjugated molecule comprising an EEC and a TC. Upon topical instillation of the ophthalmic

composition, the EEC not only increases the partition coefficient of the TC, but is believed to bind the retinal epithelium, thereby selectively targeting the TC to the retina. See e.g., *Specification*, page 11, lines 3-28.

DeSantis et al. discuss various combinations of a) a glutamate antagonist and b) an IOP (intraocular pressure) controlling agent for the treatment of glaucoma or ocular hypertension. The list of glutamate antagonists includes 6 very broad generic structures, and all isomers and pharmaceutically acceptable salts thereof (these generic structures do not include amantidines), reference to additional compounds listed in a PCT application (WO 94/13275), and a list of 14 additional compounds. The number of glutamate antagonists listed in DeSantis et al., thus number in the thousands. One of the 14 additional compounds is memantine. See DeSantis et al., page 2, paragraphs [0009] through [0018].

Likewise, DeSantis discloses that "the IOP-lowering agents useful in the present invention include all presently known IOP-lowering pharmaceuticals", including (without limitation) miotics,  $\alpha$  and  $\beta$  adrenergic agonists, beta blockers, prostaglandins, carbonic anhydrase inhibitors. See DeSantis et al., paragraph [0023]. Brimonidine is listed among such compounds.

DeSantis does not disclose and provides no reason for the person of ordinary skill to specifically select an admantidine-based glutamate antagonist for use in a combination therapy from among the exceedingly large genus of possible combinations of "glutamate antagonists". See DeSantis at ¶[0023].

But even more importantly, DeSantis does not disclose, and provides no reason for a person of ordinary skill in the art to make, a single, conjugated molecule comprising any of the IOP-controlling compounds or glutamate antagonists disclosed therein.

Collins appears to be cited by the Examiner to show that conjugated pharmaceutical agents are known. Collins does not disclose the treatment of ocular hypertension or diseases of the retina or posterior segment.

The combination of DeSantis and Collins teaches away from the present invention. As disclosed in the current specification, "the EECs of the present invention bind to the retinal epithelium. The binding of the EECs to the retinal epithelium may cause the TCs to become more bioavailable, in particular at or near the retinal epithelium." *Specification*, page 11, lines 8-12. The retinal epithelium is located in the posterior segment of the eye. Thus, the present conjugate serves to preferentially target the TC moiety of the topically applied conjugate to the posterior segment of the eye.

This fact represents a significant advance in the treatment of conditions of the posterior segment, since it is well known by those of skill in the art that ophthalmic agents tend not to migrate well to the posterior segment when topically applied to the ocular surface. As stated in the specification, many TCs may not have the proper lipophilicity to penetrate the various layers of the eye to reach the retina. *Specification* at page 10, lines 35-38.

In their December 26, 2005 Reply, the present Applicants provided data showing that the presently described prodrug conjugates are selectively targeted to melanin, which is preferentially found in the retinal epithelium located in the posterior segment of the eye, as described in the specification. These data are now being resubmitted in the Declaration of Patrick M. Hughes, Ph.D., filed herewith pursuant to 37 C.F.R. §1.132.

As outlined by Dr. Hughes in his Declaration, such selective retinal targeting would not be useful or desired in the methods and disclosure of DeSantis, since ocular hypertension, with which DeSantis is largely concerned, is a condition of the anterior segment of the eye. It is therefore critical in the disclosure of DeSantis that the IOP-lowering agents remain in the anterior segment to lower IOP (for example by decreasing the rate of aqueous humor production in the ciliary body or by increasing the rate of uveal aqueous humor outflow) and thus help to prevent mechanical "crushing" injury to the retina.

The presently claimed invention therefore functions in a completely different manner than the combination of glutamate receptor antagonists and IOP lowering agents cited by DeSantis. This difference in function would cause those familiar with DeSantis to discard the idea of making the conjugates of the present invention, since such conjugates would tend to migrate to the posterior segment, thereby defeating the purpose of the combinations disclosed by DeSantis.

Collins discloses the use of conjugates comprising an antibiotic and a vitamin B12 or intrinsic factor-binding agent targeting moiety for targeting of antibiotics to infected tissue. However, the combination of Collins and DeSantis does not lead to the compounds and compositions of the present invention. If there were any reason at all to consider conjugating the IOP lowering agents and glutamate antagonist agents of DeSantis based upon the disclosure of conjugates provided by Collins, the person of skill in the art would immediately dismiss this idea as failing to provide a solution to a major problem addressed by DeSantis; delivering an IOP lowering agent to the anterior segment of the eye.

For this reason, the combination of DeSantis and Collins teach away from the present invention. Even though Applicants do not believe that the Office Action raises a *prima facie* case of obviousness, even for cases in which the evidence adduced by the USPTO rises to such a level the Court of Appeals for the Federal Circuit indicates that "an applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect", *In re Peterson*, 315 F.3d 1325, 1331, 65 USPQ2d 1379 (Fed. Cir. 2003). Applicants submit that the present rejection is a clear example of this.

2) The combination of DeSantis and Collins provide no reason or suggestion why a person of skill in the art would make the present invention comprising a therapeutic agent and an admantidine moiety targeting the posterior segment of the eye.



In addition, DeSantis' disclosure of the treatment of glaucoma through the administration of combination of an IOP lowering agent and a glutamate receptor antagonist in no way suggests the conjugates of the presently claimed ophthalmic compositions.

To be effective, DeSantis' combinations require that upon topical administration the glutamate receptor antagonists be present within the posterior segment of the eye, where they may interact with retinal ganglion cells and optic nerve fibers to prevent damage associated with excitotoxicity. See DeSantis at ¶[0007]. At the same time, in order to be effective in the manner disclosed by DeSantis the IOP lowering agent must be present in the anterior segment of the eye (such as the uvea and the ciliary body) to reduce ocular hypertension and thus help prevent retinal damage due to mechanical, circulatory, and other poorly understood factors associated with high IOP.

In other words, as disclosed by DeSantis, the IOP lowering agent and a glutamate receptor antagonist must act in different compartments (the anterior and posterior chambers, respectively) in order to function.

In the present invention, the TC and EEC must be targeted to the same intraocular locus (the posterior segment) by virtue of being linked in a single molecule.

Like the present invention, Collins also discloses molecular conjugates. However, the person of ordinary skill in the art would not look for a way to accomplish the effect of

DeSantis by creating a single molecule comprising a TC and an EEC.

Only the present invention recognizes that the therapeutic components of the composite disclosed therein may be effective when the therapeutic agent is delivered to the posterior, rather than the anterior segment of the eye, and provides a composition effective to enhance such delivery.

For these reasons, the invention is in condition for allowance.

b) Claims 24-26.

***a) Did the examiner err by finding that the presently claimed ophthalmic compositions comprising molecular conjugates are obvious over DeSantis, which describes methods for treating conditions of the anterior segment of the eye with a combination of an IOP-lowering agent and a glutamate antagonist, and Collins, which discloses conjugates comprising antibiotic agents and a cobalamine.***

1) The combination of DeSantis and Collins teach away from a conjugate-containing ophthalmic composition comprising comprising an ophthalmically useful quinoxoline component and a covalently coupled adamantidine EEC moiety targeting the posterior segment of the eye which will deliver the conjugate to a posterior portion of an eye upon topical delivery.

Applicants incorporate by reference the arguments made with respect to claims 1-6, 8, 9, 11, 12, 14-16 above. In addition, Applicants have the following comments.

The invention of claim 24 is directed to an ophthalmic composition comprising a conjugate that includes an ophthalmically useful quinoxaline covalently linked to an EEC of a given structure, wherein the conjugate is targeted to the posterior segment of the eye upon topical delivery of the composition. Claim 25 is directed to a subgenus of quinoxalines, while claim 26 is directed to the specific quinoxaline brimonidine tartrate.

Certain ophthalmically effective quinoxoline components are useful to lower intraocular pressure. For example, DeSantis discloses that the quinoxaline compound brimonidine is a useful alpha 2 agonist IOP lowering agent. DeSantis is generally drawn to the topical application of a combination of a glutamate receptor antagonist and an IOP lowering agent for the treatment of elevated intraocular pressure.

However, as outlined in the argument above with respect to claims 1-6, 8, 9, 11, 12, and 14-16, the problem and solution disclosed by DeSantis teach away from the use of IOP agents targeted to the posterior segment of the eye. The primary ocular hypotensive mechanism of action of quinoxalines, including brimonidine, is the activation of the alpha 2 adrenoceptors in the ciliary body, thereby decreasing cyclic adenosine monophosphate(cAMP) levels and thus decreasing aqueous humor production in the anterior chamber of the eye.

DeSantis' strategy of treating elevated IOP using a glutamate receptor antagonist and an IOP lowering agent depends upon efficient delivery of the IOP lowering agent to the anterior chamber of the eye. However, the present invention

includes a conjugate compound that is specifically formulated to deliver the quinoxaline to the posterior chamber of the eye, where it may exert a neuroprotective activity. This activity is nowhere suggested in DeSantis or Collins, nor is the retinal epithelium targeting activity of the EEC of the present invention.

Collins discloses conjugates, but does not render the present invention obvious in light of DeSantis, since, unlike the present invention, Collins is not concerned with preferentially delivering compounds to the posterior segment of the eye.

Thus, the combination of DeSantis and Collins does not lead one of skill in the art to the present invention but rather directs such a person away from a composition that delivers the quinoxaline, including brimonidine, to the posterior segment rather than the anterior segment of the eye. Because of this, the combination of DeSantis and Collins do not render the invention of claims 24-26 obvious.

2) The combination of DeSantis and Collins provide no reason, or suggestion why a person of skill in the art would make the present invention comprising a ophthalmic composition comprising an ophthalmically useful quinoxoline component and a covalently coupled admantidine EEC moiety targeting the posterior segment of the eye which will deliver the conjugate to a posterior portion of an eye upon topical delivery.

Applicants incorporate by reference the arguments made with respect to claims 1-6, 8, 9, 11, 12, 14-16 above. In addition, Applicants have the following comments.

Specific IOP lowering quinoxaline compounds are alpha 2 receptor agonists that are believed to act on the alpha 2 adrenoreceptors located in the ciliary body of the eye to reduced aqueous humor outflow, thereby decreasing IOP. The ciliary body is located in the anterior chamber of the eye.

The combination of DeSantis and Collins provide absolutely no reason for the person of ordinary skill in the art to make ophthalmic compositions comprising the presently disclosed conjugates. The teachings of DeSantis would not lead, even in light of the disclosure of antibiotic/vitamin B12 conjugates disclosed by Collins, the person of ordinary skill in the art to opt to make a topical ophthalmic composition comprising a quinoxaline - admanidine conjugate to target the posterior segment of the eye. This is particularly true when the targeting of retinal epithelial tissue by the admanidine moiety of the conjugate appear to defeat the object of DeSantis to provide IOP lowering activity (which is provided in the anterior segment ciliary body for the alpha 2 agonist quinoxalines) in the combination therapy it discloses.

For these reasons, Applicant respectfully ask the Board to reverse the Examiner's contention that claims 24-26 are obvious in view of DeSantis and Collins.

**CONCLUSION**

For the foregoing reasons Applicants respectfully request that the Board affirm the patentability of the pending claims, as amended in the Rule 42.33 Amendment filed July 7, 2006, by reversing the Examiner's holding of obviousness. Each of the claims has been argued separately, thus the claims each stand or fall independently of the other claims.

Applicants have filed herewith either a check or deposit account authorization for payment of the fee associated with the filing of this Appeal Brief. If any other fee is due, Applicants hereby authorize the Commissioner to use Deposit Account 01-0885 for the payment of such fee.

Respectfully submitted,

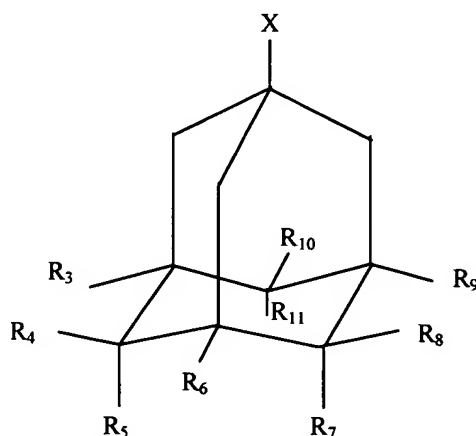
A handwritten signature in black ink, appearing to read "Carlos A. Fisher". The signature is fluid and cursive, with the first name "Carlos" being the most prominent part.

Carlos A. Fisher  
Reg. No. 36,510  
Attorney for Applicants

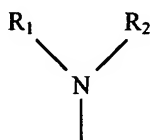
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CLAIM APPENDIX

1. (Previously presented) A topical ophthalmic composition comprising a carrier and a pharmaceutical conjugate comprising an ophthalmically useful therapeutic component covalently coupled to an efficacy enhancing component effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye, the efficacy enhancing component having the formula A:



wherein X is



R1, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 are independently an H, a C1-C10 hydrocarbon, or a linker.

2. (Previously presented) A composition of claim 1 wherein the therapeutic component and the efficacy enhancing component

are directly joined by a covalent bond, and the carrier comprises a liquid.

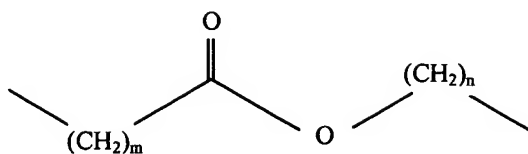
3. (Previously presented) A composition of claim 1 wherein the therapeutic component and the efficacy enhancing component are joined by a linker.

4. (Previously presented) A composition of claim 1 wherein R1 and R2 are Hs, and R3 is a linker.

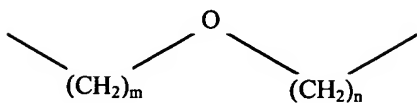
5. (Previously presented) A composition of claim 1 wherein the efficacy enhancing component is a memantine.

6. (Previously presented) A composition of claim 1 wherein the linker is selected from the group consisting of:

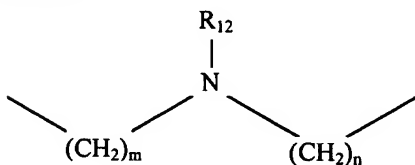




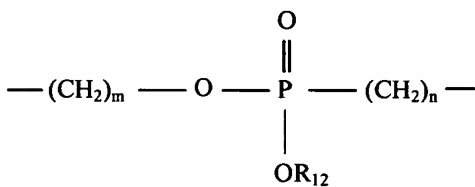
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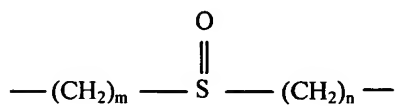
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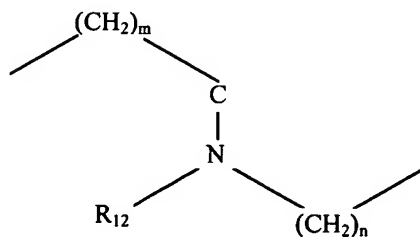
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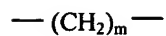
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Linker H

wherein R12 is an H or a C1-C10 hydrocarbon, m = 0 to 10, and n = 0 to 10.

7. (Withdrawn) A pharmaceutical conjugate of claim 1 wherein the therapeutic component is selected from the group consisting of NMDA antagonists, antibacterials, antihistamines, decongestants, antiinflammatories, antiparasitics, miotics, anticholinergics, adrenergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives, muscle relaxants, diagnostics, tyrosine kinase inhibitors and neuroprotectants.

8. (Previously presented) A composition of claim 1 wherein the therapeutic component is selected from the group consisting of quinoxaline, (2-imidazolyl-2-ylamino) quinoxaline, 5-bromo-6-(2-imidazolyl-2-ylamino) quinoxaline, and mixtures thereof.

9. (Previously presented) A composition of claim 1 wherein the efficacy enhancing component comprises a memantine, and the conjugate further comprises a linker joining the therapeutic component and the memantine.

10. (Withdrawn) A pharmaceutical conjugate of claim 1 wherein the therapeutic component comprises a timolol and the efficacy enhancing component comprises a memantine, and the conjugate further comprises a linker joining the timolol and the memantine.

11. (Previously presented) A composition of claim 8 further comprising a memantine, and a linker joining the therapeutic component and the memantine.

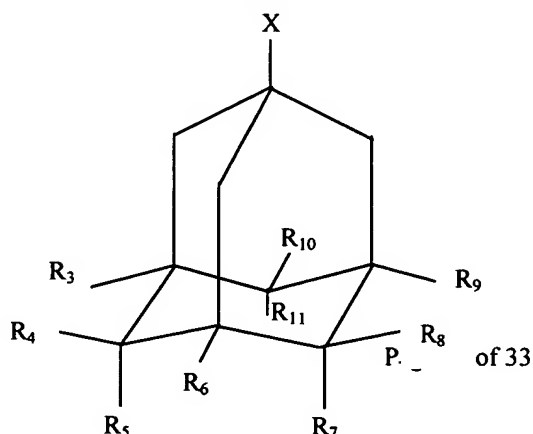
12. (Previously presented) A composition of claim 1 wherein the therapeutic component and the efficacy enhancing component disassociate under physiological conditions.

13. (Cancelled)

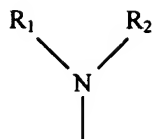
14. (Previously presented) A composition of claim 1 wherein the conjugate has an aqueous solubility, a partition coefficient and/or an affinity for melanin that is greater relative to a compound comprising the same therapeutic component which is not joined to an efficacy enhancing component.

15. (Previously presented) A composition of claim 1 wherein the conjugate is a salt.

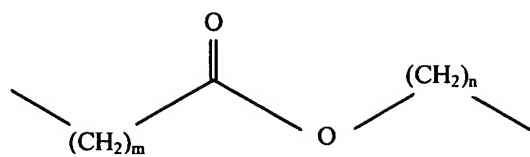
16. (Previously presented) A topical ophthalmic composition comprising a carrier and a pharmaceutical conjugate comprising an ophthalmically useful therapeutic component covalently coupled to an efficacy enhancing component effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye, the efficacy enhancing component having the formula A:



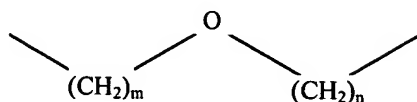
wherein X is



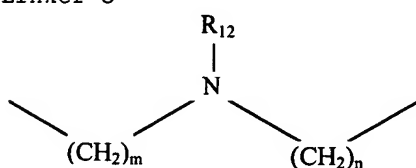
R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> are independently an H, a C<sub>1</sub>-C<sub>10</sub> hydrocarbon, or a linker; the linker is selected from the group consisting of:



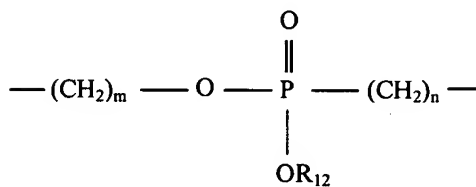
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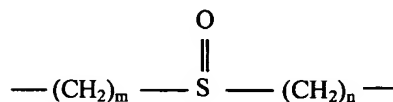
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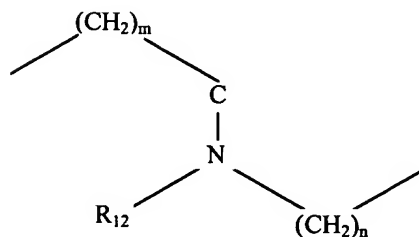
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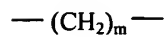
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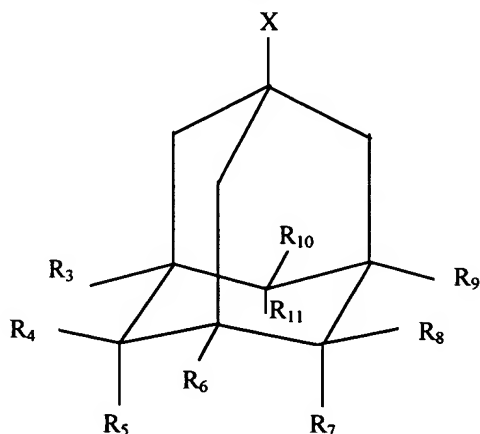


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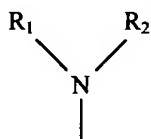
wherein R12 is an H or a C1-C10 hydrocarbon,  $m = 0$  to 10, and  $n = 0$  to 10.

17-23. (Cancelled)

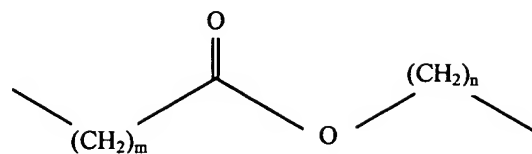
24. (Previously presented) An ophthalmic composition comprising a carrier and a pharmaceutical conjugate comprising an ophthalmically useful quinoxoline component-containing therapeutic component covalently coupled to an efficacy enhancing component effective in delivering the conjugate to a posterior segment of an eye of an individual when the composition is topically administered to the eye, the efficacy enhancing component having the formula A:



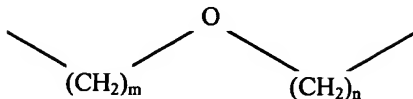
wherein X is



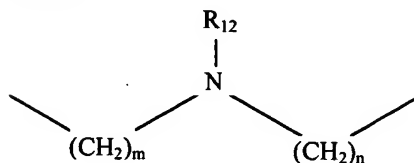
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 are independently an H, a C1-C10 hydrocarbon, or a linker; the linker is selected from the group consisting of:



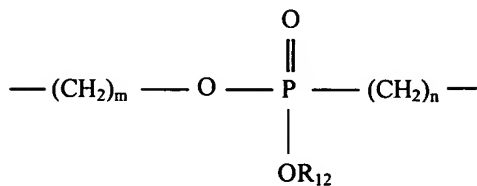
Linker B



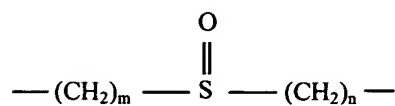
Linker C



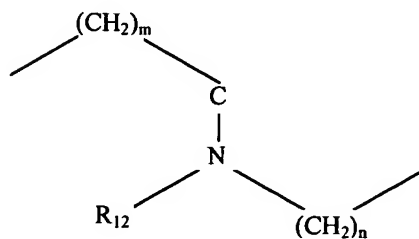
Linker D



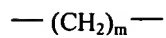
Linker E



Linker F



Linker G



Linker H

wherein R12 is an H or a C1-C10 hydrocarbon,  $m = 0$  to 10, and  $n = 0$  to 10.

25. (Previously presented) The composition of claim 24 wherein the therapeutic component is selected from the group consisting of quinoxaline, (2-imidazolyl-2-ylamino) quinoxaline, 5-bromo-6-(2-imidazolyl-2-ylamino) quinoxaline, and mixtures thereof.

26. (Previously presented) The composition of claim 25 wherein the therapeutic component comprises brimonidine tartrate.



**EVIDENCE APPENDIX**

1. Declaration of Patrick M. Hughes, Ph.D.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Appl. No. : 10/016,850 Confirmation No. 7435  
Applicant : HUGHES et al.  
Filed : December 14, 2001  
Title : PHARMACEUTICAL CONJUGATES WITH ENHANCED  
PHARMACOKINETIC CHARACTERISTICS

TC/A.U. : 1600/1618  
Examiner : FAY, Z.

Docket No. : D-3004  
Customer No. : 33197

**Mail Stop Non-Fee**  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION OF PATRICK HUGHES Ph.D. (37 CFR § 1.132)**

Dear Sir,

I, Patrick Hughes, Ph.D., am an inventor of the subject matter claimed in United States Patent Application Serial No: 10/016,850, and I hereby make the following declaration.

1. I received a Bachelor of Science degree in Pharmacy from the St. Louis College of Pharmacy in 1989. I was awarded a Ph.D. from Purdue University in 1995, by the School of Pharmacy and Pharmaceutical Sciences. My research project concerned the transcorneal ocular delivery of acycloguanosine analogues and evaluation of

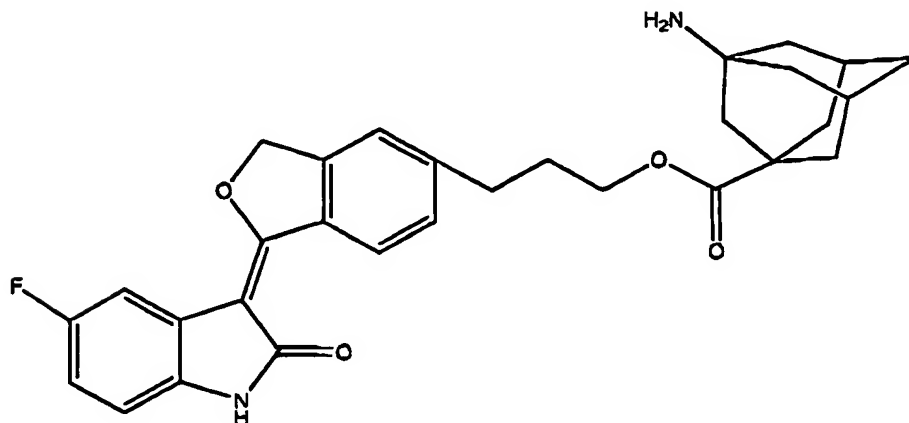
the compounds both in vitro and in vivo using a rabbit model.

2. From 1989 to 1991 I was a teaching assistant (Clinical Pharmacokinetics) in the School of Pharmacy and Pharmaceutical Sciences, Purdue University. From 1989 to 1995 I was a Graduate Research Assistant in the School of Pharmacy and Pharmaceutical Sciences, Purdue University, where I did extensive development of analytical methods using High Performance Liquid Chromatography to study drug metabolism, and developed animal models for the study of ocular delivery of drugs.
3. I have received numerous awards and fellowships for my studies in drug delivery. Additionally, I am an author of a number of scientific papers concerning ocular drug delivery. Most recently I have co-edited an edition of Advanced Drug Delivery Reviews "Drug Delivery Strategies to Treat Age-Related Macular Degeneration", P. M. Hughes and O. Olejnik eds. Volume 57, Issues 14, 13 December 2005.
4. From 1995 to present I have been employed at Allergan, Inc. I have been responsible for predevelopment, formulation development and preformulation. In these roles I have served as CMC Team leader and Global Project Team leader for several drug delivery projects. I am currently Director of Preformulation and will take over the role of Director, Early Development in January 2007.
5. I understand that the present patent application has been rejected as allegedly unpatentable under 35 U.S.C.

§103(a) over the combination of DeSantis (U.S. Patent Publication 2001/0047012), which discusses the combined topical use of a glutamate antagonist and an intraocular pressure (IOP) lowering agent for the treatment of glaucoma and ocular hypertension and Collins et al., (WO 01/92288), which discloses the use of antibiotic/vitamin B12 conjugate for targeted therapy and imaging of infections.

6. The combined topical use of a glutamate antagonist and an intraocular pressure (IOP) lowering agent disclosed by DeSantis requires that the IOP lowering agent is substantially localized in the anterior chamber of the eye, wherein it may exert its ocular hypotensive activity, thus helping prevent mechanical "crushing" ischemic damage to the retina caused by high IOP.
7. The present invention comprises an ophthalmic composition containing a conjugate that includes an adamantane-based targeting moiety and a therapeutic component. The targeting moiety directs the therapeutic component to the retinal epithelium (located in the posterior rather than the anterior segment of the eye), as demonstrated in the following experiment.
8. In the eye, melanin is found in the cells of the retinal epithelium located in the posterior segment of the eye and in the iris. The conjugates of the present invention will preferentially deliver the therapeutic agent to the posterior segment in an amount at least several fold that delivered to the anterior segment. To show the selective binding of these conjugates to

melanin, the following compound (a tyrosine kinase inhibitor bound to adamantaneamine), designated Compound A and comprising an embodiment of the claimed compositions in the present patent application, was synthesized:



9. A melanin binding study was conducted using Compound A. Concentrations of Compound A ranging from 5  $\mu$ M to 40  $\mu$ M were incubated with 1 mg/ml of melanin in deionized water. After 15 minutes incubation, Compound A was almost entirely bound to the melanin after 15 minutes at all tested concentrations, indicating that saturation of the melanin by the prodrug had not been reached. The data are shown in Table 1, shown below. The binding of the adamantineamine moiety of the conjugate to melanin was rapid, reaching equilibrium within an incubation time of 15 minutes.

**Table 1. Bound Concentrations of Compound A in 1 mg/ mL Sepia Melanin**

Compound A Conc. ( $\mu\text{M}$ )	Compound A Free ( $\mu\text{M}$ )	Compound A Bound ( $\mu\text{M}/\text{mg}$ )
4.98	1.42	3.56
9.95	1.42	8.53
19.90	1.47	18.43
29.85	1.61	28.24
59.69	1.65	58.04

10. Another experiment used a lower concentration of melanin in an attempt to determine saturation concentrations of Compound A, in vitro. Under similar conditions as in the previously described experiment, 0.02 mg/ml of melanin was incubated with Compound A at concentrations ranging from 10 to 40  $\mu\text{M}$ . Again, the amount of Compound A bound to the melanin was a function of the amount added to the incubation mixture at all concentrations, thus indicating that saturation had not yet occurred. The data is shown in Table 2.

**Table 2. Bound Concentrations of Compound A in 0.02 mg/ mL Sepia Melanin**

Compound A Conc. ( $\mu\text{M}$ )	Compound A Bound ( $\mu\text{M}/\text{mg}$ )
10.25	9.01
20.5	15.9
30.74	23.25


40.99	30.48
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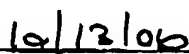
11. Therefore, these experiments show that the compounds of the present invention have the ability to quickly and selectively bind melanin, a compound found in high concentrations in the retinal-pigmented epithelial (RPE) cells located in the posterior segment of the eye. Because of this selective binding capacity, this experiment thus shows that the prodrugs of the present invention have the ability to target the RPE cells of the posterior segment of the eye, and thereby direct the therapeutic component portion of the product to the posterior segment.
12. Thus, in the event that an embodiment of the conjugates of the present invention were to comprise a conjugate of DeSantis' a glutamate antagonist and IOP lowering agent, the IOP lowering activity of the latter agent would be expected to be compromised by virtue of its targeting to the posterior segment. For this reason, DeSantis addresses a materially different problem and solution than the present invention, which the person of ordinary skill in the art would not expect to work, nor in my opinion would it work, in the manner described by DeSantis for the treatment of ocular hypertension and glaucoma.
13. Collins merely discloses conjugates comprising antibiotics and a targeting moiety that directs the antibiotic to infected tissue. Unlike the presently claimed prodrugs, the conjugates of Collins would not

preferentially direct therapeutic components to the retinal epithelium or the posterior segment of the eye.

14. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the present application or any patent issuing thereon.

Respectfully submitted,

  
\_\_\_\_\_  
Patrick M. Hughes, Ph.D.

  
\_\_\_\_\_  
Date